

What is Claimed is:

1. A mixture of conjugates, each conjugate comprising a calcitonin coupled to at least one oligomer through an amine function of the calcitonin, wherein the mixture is a monodispersed mixture, a substantially purely monodispersed mixture or a purely monodispersed mixture and the oligomer comprises a polyethylene glycol moiety.
- 5 2. The mixture according to claim 1, wherein the polyethylene glycol moiety has at least 2 polyethylene glycol subunits.
3. The mixture according to claim 1, wherein the conjugates have the capability
10 of lowering serum calcium levels by at least 5 percent.
4. The mixture according to claim 1, wherein the conjugates have an increased resistance to degradation by chymotrypsin or trypsin when compared to the resistance to degradation by chymotrypsin or trypsin of the calcitonin which is not coupled to the
15 oligomer.
5. The mixture according to claim 1, wherein the conjugates have a bioefficacy that is greater than the bioefficacy of the calcitonin which is not coupled to the oligomer.
- 20 6. The mixture according to claim 1, wherein the calcitonin is covalently coupled to the oligomer by a hydrolyzable bond, a non-hydrolyzable bond or both.
7. The mixture according to claim 1, wherein the calcitonin is covalently coupled to the polyethylene glycol moiety of the oligomer.
- 25 8. The mixture according to claim 1, wherein the oligomer further comprises a lipophilic moiety.
9. The mixture according to claim 1, wherein each oligomer has the same
30 molecular structure.
10. The mixture according to claim 9, wherein the calcitonin, polyethylene glycol moiety or both is covalently coupled to the lipophilic moiety.

11. The mixture according to claim 1, wherein the conjugates are each amphiphically balanced such that each conjugate is aqueously soluble to penetrate biological membranes.

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12. A composition comprising:
the mixture according to claim 1; and
a pharmaceutically acceptable carrier.

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13. A method of treating a bone disorder in a subject in need of such treatment, said method comprising administering an effective amount of a mixture of conjugates according to claim 1 to the subject to treat the bone disorder.

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14. The method according to claim 13, wherein the bone disorder is osteoporosis
Paget's disease, or hypercalcemia.

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15. A mixture of conjugates, wherein each conjugate comprises a calcitonin coupled to an oligomer that comprises a polyethylene glycol moiety having at least 4 polyethylene glycol subunits, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

16. A mixture of conjugates each comprising a calcitonin coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

wherein:

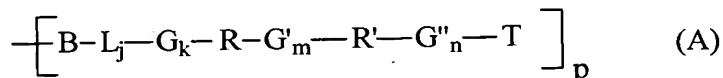
n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

17. The mixture of conjugates according to claim 16, wherein the dispersity coefficient is greater than 100,000.

18. A mixture of conjugates in which each conjugate has the same molecular weight and has the structure: Calcitonin drug-oligomer, where the oligomer has the formula:



wherein:

the Calcitonin drug is a salmon calcitonin;

B is a bonding moiety;

L is a linker moiety;

G, G' and G'' are individually selected spacer moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety;

j, k, m and n are individually 0 or 1; and

p is an integer from 1 to the number of nucleophilic residues on the calcitonin drug.

19. A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising a calcitonin coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula I:



wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive ion,

with a substantially monodispersed mixture comprising compounds having the structure of Formula II:



wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,

under conditions sufficient to provide a substantially monodispersed mixture comprising polymers having the structure of Formula III:



activating the substantially monodispersed mixture comprising polymers of Formula III to provide a substantially monodispersed mixture of activated polymers capable of

reacting with a calcitonin; and

reacting the substantially monodispersed mixture of activated polymers with a calcitonin under conditions sufficient to provide a substantially monodispersed mixture of conjugates each comprising a calcitonin coupled to an oligomer that comprises a polyethylene glycol moiety with m+n subunits.

20. The process according to claim 19, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with a calcitonin.